NTP researchers win International Society for Neurochemistry recognition

By Heather Franco

While a trip to Cancun may mean a vacation to many, for scientists in the NTP Laboratory Neurotoxicology Group at NIEHS, headed by Jean Harry, Ph.D., it marked an opportunity to present their scientific work and participate in an extraordinary experience with leaders in their field. Biologist Chris McPherson, Ph.D., and visiting fellow Ruben Orihuela, Ph.D., earned places in the highly competitive International Society for Neurochemistry (ISN) Advanced School *(http://www.neurochemistry.org/meetings/isn-advanced-school.html)* April 16-20.

Along with some 1,000 scientists, they also attended the biennial meeting of ISN April 20-24, held jointly with the American Society for Neurochemistry (ASN).

As part of their experience at the ISN Advanced School, the members of the Neurotoxicity group presented posters detailing their recent scientific works (see text box). McPherson's work was honored with a top ISN Advanced School award for poster presentations.

Rare experience yields valuable opportunities

"Participating in the ISN Advanced School was my most unique science training experience," said McPherson. This prestigious opportunity provides support and training for 70 graduate students and new Ph.D. scientists in the field of neurochemistry.

"I was ecstatic for both of them to be selected for the school," said Harry. "It is rare to have two students selected from the same laboratory." This honor speaks not only to the quality of both junior scientists, but also to the mentoring of lead investigator Harry.

The researchers participated in seminars detailing the current state of the field of glial-neuronal interactions. In addition, they were able to present and discuss their own work in an informal setting. "Because of the small size and international attendance, the school gave me the opportunity to interact with both junior and senior investigators from all over the world in a more intimate setting," explained Orihuela. The study presented by Orihuela prompted a solicitation for manuscript submission by an editor of a special issue of the British Journal of Pharmacology. This confirmed to Orihuela the value of such interactions for visibility of one's work.

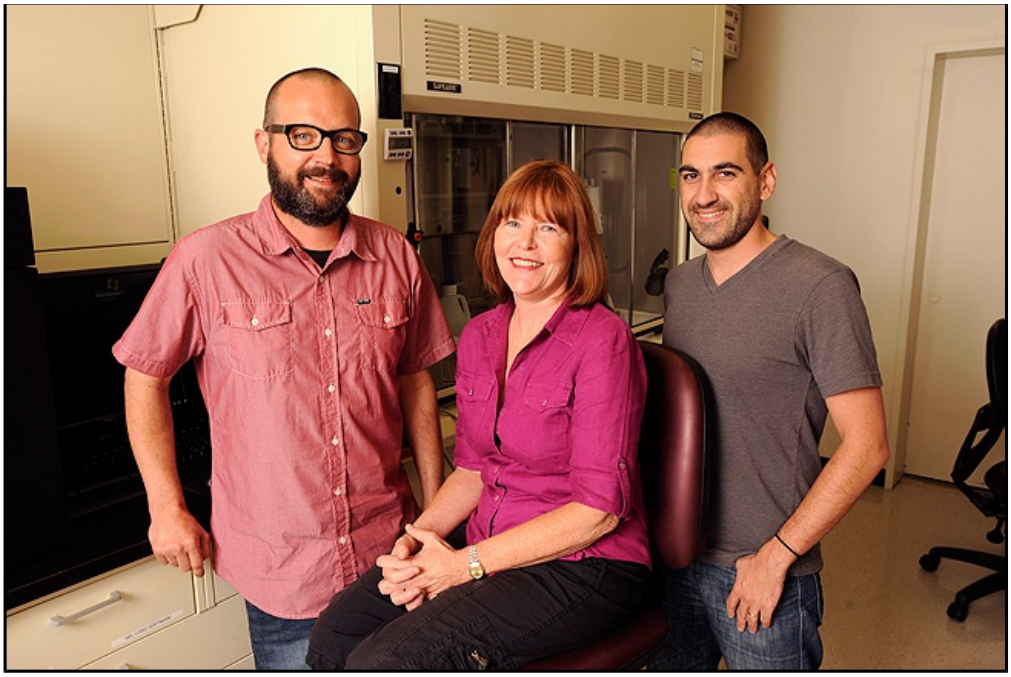
Both McPherson and Orihuela were able to make connections that will enhance their future careers. McPherson has aspirations to continue his studies integrating environmental exposures with human health issues. Orihuela strives to bring his cross-disciplinary approach to a research team at a premier university or research center.

Enhancing both their science and career paths

"Participating in these types of activities provides trainees with experiences that will enhance their scientific endeavors and their future career paths," said Harry. Both McPherson and Orihuela appreciated the opportunity to attend these events.

"Thanks to the support of both Jean and NIEHS, I was able to attend this school and magnificent conference, where I was able to interact with, and present my work to, the leaders in my field," states Orihuela. "It is great working for a mentor who values and encourages us to take advantage of these types of training opportunities," confirms McPherson. Both agree it is this focus on overall training that has led to the success of the group.

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Reproductive Developmental Biology Group.)



Shown in their lab at NIEHS are members of the Harry Group, left to right, McPherson, Harry, and Orihuela. (Photo courtesy of Steve McCaw)

Understanding the role of inflammation following neuronal injury

As Harry explained, “Injury to the neurons of the hippocampus can have detrimental effects on brain function and result in conditions such as Alzheimer’s disease and epilepsy.” To resolve these injuries, specialized macrophages, called microglia, produce inflammatory factors to aid in the repair process. “Microglia exist in two states — pro-inflammatory M1 and anti-inflammatory M2 — which produce a unique set of inflammatory factors,” she said.

Orihuela — characterizing the microglia population

Orihuela sought to better understand these two microglial states using an *in vitro* microglial cell line. Upon differentiation of the cells to the M1 state, he found an increase in the expression of oxidative stress genes, nitric oxide levels, and reactive oxygen species. The cells also showed a decrease in basal respiration and an increase in the acidification rate. Together these results demonstrate a change in the bioenergetic profile of the mitochondria, consistent with increased oxidative stress. These responses were not observed upon differentiation to the M2 state. Thus, these distinctions in mitochondrial bioenergetics of the M1 and M2 microglia may help explain the different phenotypes of these two states.

McPherson — an environmental exposure model of neuronal injury

In his award-winning experiments, McPherson investigated the role of the M1 and M2 inflammatory factors in the repair process following brain injury. He used a model in which the hippocampal toxicant trimethyltin (TMT) was administered to mice. “Exposure to this toxicant in mice causes hippocampal injury similar to Alzheimer’s disease,” McPherson explained. “Using this model system, we are able to examine the contribution and shift of the various M1/M2 states of the brain macrophages.” He found that with the onset of neuronal death and phagocytosis, microglia display an M1 stage of activation, and that a shift to the M2 repair phase was critical for promoting the brain to generate new neurons to replace those lost in the hippocampus. Therefore, each of the stages provided a critical step for the full process, and suggested a shift to the M2 phenotype to facilitate the differentiation of stem/progenitor cells to neurons. He is continuing this work to identify the nature of the trigger for this shift.

Insights into the causes of neurodegenerative diseases

Combining the mechanistic data from Orihuela’s work, with the functional data from McPherson’s research, these studies provide a new understanding of the microglia state following brain injury. "We use TMT as a chemical tool to understand the processes associated with neuroinflammation and adult neurogenesis,” McPherson said. “While TMT is not currently in use in the United States, other countries, such as those on the Asian continent, still use TMT commercially as a polyvinyl chloride heat stabilizer and in biocides.”

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